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REMARKS

Claims 72-91 are pending in the present application. Claims 72-91 are rejected under 35 U.S.C. § 103(a). Applicants respectfully disagree with the rejection and submit the following remarks in response thereto.

Rejection Under 35 U.S.C. § 103

Claims 72-74, 77-87, and 89-91 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Vitiello et al., U.S. Patent No. 6,419,931 B1 (Vitiello) in view of Kundig et al., *Science* 268:1343-47 (1995) (Kundig). Specifically, the Office Action asserts that Vitiello discloses a method of inducing and maintaining a CTL response in a mammal. The Office Action argues that although Vitiello does not disclose administering the antigen directly to the lymphatic system, Kundig teaches the step of delivering antigen directly to the lymphatic system, and it would have been obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Kundig in the method of Vitiello in order to efficiently elicit a CTL response.

Claims 72, 73, 75, 76, 87, and 88 were further rejected under 35 U.S.C. § 103(a) as being unpatentable over Bot et al., U.S. Patent No. 6,204,250 B1 (Bot) in view of Kundig. Specifically, the Office Action asserts that Bot discloses a method of inducing and maintaining a CTL response in a mammal. The Office Action notes that "Diamond doesn't disclose administering the antigen directly to the lymphatic system." Applicants presume that the Office Action intended reference to Bot and not Diamond. The Office Action further argues that Kundig teaches the step of delivering antigen directly to the lymphatic system and it would have been obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Kundig in the method of Bot in order to efficiently elicit a CTL response.

Applicants disagree with the rejection and submit that the pending claims are allowable over these references.

A necessary criterion in establishing a *prima facie* case of obviousness is that the cited "reference (or references combined) must teach or suggest all the claim limitations." M.P.E.P.

§ 2142 (citing *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991)). In evaluating the patentability of any claim against the cited references, "all words in [the] claim must be considered." *In re Wilson*, 424 F.2d 1382 (CCPA 1970); M.P.E.P. § 2143.03.

The claims of the instant application are all directed to obtaining a sustained CTL response. The term "sustained CTL response" is a meaningful feature of the claims, and thus, must be considered in evaluating the patentability of the instant application against the cited references.

The use of the term "CTL response" is generally understood by those of skill in the art to refer to CTL possessing cytolytic activity, namely, effector CTL (*see, e.g.*, Vitiello, at col. 11, lines 29-31), and not merely to an increase in the number of cells that could acquire cytolytic activity upon stimulation or restimulation with antigen, namely, naïve CTL and memory CTL. The use of the term "CTL response" to refer to CTL possessing cytolytic activity is clear in the instant application. For example, the specification discloses that indicators of a CTL response include: (1) a skin test dependent on the presence of highly activated CTL (Specification, at page 12, lines 6-10); (2) specific T-cell frequencies elevated orders of magnitude above a "memory" level (Specification, at page 13, lines 1-5); and (3) positive primary *ex vivo* cytotoxicity (*see, e.g.*, Specification, at page 61, lines 24-29). (Emphasis added.)

Typically, during the effector CTL phase of the cytolytic immune response, the population of effector CTL circulating in the body rapidly expands and then diminishes following exposure to antigen, typically peaking after about 7-10 days. If the typical response dynamics of the population of effector CTL were to be depicted graphically, the graph would show a curve of increasing population or activity with a peak at 7-10 days and a rapid decline from that peak.

The term "sustained CTL response" would be recognized by those of skill in the art to refer to a prolonged phase of effector CTL in the cytolytic immune response. In a sustained CTL response, the population of effector CTL following exposure to antigen can be graphically represented as an increase and subsequent plateau, rather than the typical initial increase to a peak followed by a rapid decline. Applicants' claims are all directed to a sustained CTL response, which sustained response is not taught or suggested in Vitiello, Bot, or Kundig.

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1. Vitiello does not teach or suggest obtaining a sustained CTL response.

VITIELLO teaches inducing or stimulating a CTL response using a composition comprising a combination of a peptide constituting a CTL epitope, a peptide constituting an HTL epitope, wherein one of the peptides is lipidated and/or the composition further comprises an adjuvant, using conventional routes of administration. The specification contemplates multiple administrations of the composition that might continue periodically until an infection is resolved, which is presented in the context of a classic booster immunization regimen (col. 21, lines 18-21). Specifically, Vitiello states, that "boosters are spaced a[t] sufficient interval[s] apart to optimize development of a CTL response to the antigen of interest, e.g., a second administration may be approximately four weeks after the initial administration." Vitiello et al., at col. 4, lines 60-63.

In conventional boosting immunization protocols the CTL response disappears between doses, the effector CTL having either undergone apoptosis or conversion to memory CTL. Vitiello does not teach or suggest prolonging the effector phase of the cytolytic immune response between doses. In addition, Vitiello reports CTL responses in terms of magnitude without any reference to the duration of such responses. Finally, the secondary assays reported in Vitiello fail to indicate the prolongation of the effector CTL phase of the cytolytic immune response between doses. Thus, a person of ordinary skill in the art would recognize that Vitiello does not teach or suggest a sustained CTL response.

2. Bot does not teach or suggest a sustained CTL response.

Bot teaches prophylactic immunization of infants in which an initial immunization using nucleic acid antigen is followed some time later by a booster immunization with live virus. Bot *et al.*, at col. 8, lines 27-29. The number of inoculations required for the induction of the described effect using the method taught by Bot is "at least one, and is more preferably three" inoculations. Bot, at col. 8, lines 39-44, and col. 9, lines 55-56. Bot does not teach or suggest prolonging the effector CTL phase of the cytolytic immune response between inoculations.

Bot discloses that primary cytotoxicity was observed only after the booster immunization with live virus. *Id.* at col. 11, lines 56-64. However, Bot provides no disclosure of the post-peak

phase of the CTL response following the booster immunization with live virus. In addition, the virus challenge experiments disclosed in Bot, at col. 12, line 26 to col. 13, line 13, are relevant to immunity resulting from the presence of memory CTL, but are not indicative of a sustained CTL response, which requires the presence of effector CTL. Thus, Bot does not disclose prolonging the effector CTL phase of a cytolytic immune response. Accordingly, one of ordinary skill in the art would recognize that Bot does not teach or suggest a sustained CTL response.

3. Kundig does not teach or suggest obtaining a sustained CTL response.

Kundig discloses the induction of a CTL response using fibroblasts as antigen presenting cells (APCs). Specifically, Kundig discloses that "mice injected with fibroblasts expressing viral proteins developed strong antiviral cytotoxic T lymphocyte (CTL) responses, without any involvement of professional APCs." Kundig *et al.*, at 1343. Kundig further discloses that "fibroblasts induced T cell responses only when they reached the lymphoid organs." *Id.*

Kundig concludes that "cells other than professional APCs can directly induce T-cells." *Id.* Namely, Kundig concludes that fibroblasts can function as immunogenic APCs if located in the lymphoid organs. *Id.* at 1346. Kundig theorizes that "transport of antigen into lymphoid organs is not only necessary but is sufficient for immunogenic APC function, whereas costimulatory properties do not have to be directly linked to this cell." *Id.*

While Kundig teaches the induction of a CTL response using transfected fibroblasts expressing viral peptides, Kundig does not teach or suggest obtaining a sustained CTL response. The secondary assays used by Kundig to detect a CTL response provide no indication of the duration of the resulting CTL response. Furthermore, Kundig provides no discussion, teaching, or suggestion regarding the prolongation of the resulting CTL response. Because Kundig concerns only the induction of a CTL response, one of skill in the art would recognize that Kundig does not teach or suggest a sustained CTL response.

Because the same feature of the claimed invention, namely, a sustained CTL response, is missing from each of the cited references, it necessarily follows that there is no combination of the references that teaches or suggests this feature. Thus, the cited references, either alone or in combination, do not teach or suggest obtaining a "sustained CTL response." Accordingly, both

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the combination of Vitiello in view of Kundig and the combination of Bot in view of Kundig fail to satisfy a necessary criterion for establishing a *prima facie* case of obviousness.

For the foregoing reasons, the Office Action has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 72-74, 77-87, and 89-91 under 35 U.S.C. § 103 as being unpatentable over Vitiello in view of Kundig. Likewise, Applicants respectfully request withdrawal of the rejection of Claims 72-74, 77-87, and 89-91 under 35 U.S.C. § 103 as being unpatentable over Bot in view of Kundig.

CONCLUSION

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding Office Action are erroneous and that the application is now in condition for allowance.

Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is respectfully requested to call the undersigned to discuss such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: August 6, 2003

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